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The Cells of Cajal-Retzius: Still a Mystery One Century After

Minireview

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Cajal-Retzius (CR) cells are an enigmatic class of neurons located at the surface of the cerebral cortex, playing a major role in cortical development. In this review, we discuss several distinct features of these neurons and the mechanisms by which they regulate cortical development. Many CR cells likely have extracortical origin and undergo cell death during development. Recent genetic studies report unique patterns of gene expression in CR cells, which may help to explain the developmental processes in which they participate. Moreover, a number of studies indicate that CR cells, and their secreted gene product, reelin, are involved in neuronal migration by acting on two key partners, migrating neurons and radial glial cells. Emerging data show that these neurons are a critical part of an early and complex network of neural activity in layer I, supporting the notion that CR cells modulate cortical maturation. Given these key and complex developmental properties, it is therefore conceivable for CR cells to be implicated in the pathogenesis of a variety of neurological disorders.

More than a century after the discovery by S. Ramon y Cajal and G. Retzius, CR cells continue to be the focus of much research effort. This interest can be attributed to several factors. On one hand, these cells are exclusively and strategically localized at the surface of the entire cerebral cortex during most of the cortical development to regulate a number of developmental processes (Marin-Padilla, 1998). On the other hand, the finding that reelin is highly expressed by CR cells has allowed researchers to use reelin as a marker to study the biology of these neurons. However, in spite of recent advances, many aspects of the cell biology of these neurons remain to be fully elucidated. In this review, we will discuss selected aspects of the intriguing biology of CR cells.

Too Many Origins for Just One Fate?

CR cells cover the entire cortex very early in development (including the archicortex), long before the formation of the cortical plate, and appear in distinct regional gradients. Traditionally, it has been thought that CR cells originate in the cortical ventricular zone, similar to the remaining cortical neurons except GABAergic interneurons. However, more recent data, including gene expression mapping studies and cell lineage tracing analyses, indicate that CR cells may originate at specific and precise production sites, from where they migrate tangentially through layer I, in a similar way to the tangential migration of GABAergic interneurons. The regions that have been proposed as origins of CR cells include extracortical areas, such as the periolfactory forebrain, and selected portions of the cortical anlage and related areas, such as the cortical hem, taenia tecta, or the caudomedial wall of the telencephalon (Hevner et al., 2003; Meyer et al., 2002; Takiguchi-Hayashi et al., 2004; Yamazaki et al., 2004). In addition, it has been suggested that the ganglionic eminence may give rise to a subset of CR cells, which at least in humans may express some basal forebrain genes (Rakic and Zecevic, 2003). It is noteworthy, however, that CR cells express a number of transcription factors, such as Tbr1 and Emx1/2, that are specific to the cortical proliferative ventricular zone (Boncinelli et al., 2000; Gorski et al., 2002; Hevner et al., 2001; Shinozaki et al., 2002). Moreover, the recent finding that the inactivation of the Foxg1 gene in cortical ventricular zone progenitors directs these cells to be converted to CR cells indicates that these progenitors also have the potential to give rise to these neurons (Hanashima et al., 2004). These studies together suggest that CR cells have distinct sites of origin, although additional cell lineage-based studies are required to elucidate their exact contribution to the CR cell population.

Simultaneous production of CR cells at several sites may guarantee a fast and complete coverage of all the regions of the cerebral cortex by these neurons, thereby ensuring that these cells are in the correct position to accomplish their crucial functions in development. In addition, multiple origins and migration routes may facilitate regional- and cell-specific specification of CR cells.

After the initial controversy, probably caused by the misclassification of CR cells, it is now clear that, normally, most of these neurons are eliminated through cell death. In rodents, for example, using several methods such as cell counting and BrdU tracing, it has been estimated that more than 95% of CR cells die after the first postnatal week, once neuronal migration has been completed (del Rio et al., 1995; Derer and Derer, 1990; Super et al., 1998). In monkeys and humans, similar estimates of CR cell loss have also been reported to occur directly after migration (Abraham and Meyer, 2003; Abraham et al., 2004; Zecevic and Rakic, 2001). Therefore, although there are regional differences in the cell death process (most notably in the hippocampus), CR cells are a population of transient neurons, contributing to the building of cerebral cortex at specific developmental stages. Although the normal timing of Cajal-Retzius cell death is altered by manipulating neural activity, by incubation with neurotrophic factors, and also in a number of lesions, little is known about the mechanisms that trigger this naturally occurring cell death process (Benardete and Kriegstein, 2002; Del Rio et al., 1996; Eriksson et al., 2001; Marty et al., 1996). In this context, a future research challenge would be to examine whether the manipulation of CR cell life span affects migration capacity in the late postnatal cerebral cortex.

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Role of the Cajal-Retzius Cell in Migration: To Go or Not to Go

The function of CR cells has been challenged by the findings that these neurons are the main source of reelin production in cortical development (D'Arcangelo et al., 1995; Rice and Curran, 2001; Tissir and Goffinet, 2003). The absence of reelin, a large extracellular protein, leads to devastating effects on neural migration, including abnormal migration and positioning, with a resulting pattern of altered lamination in the cerebral cortex. Moreover, in *reeler* mice, the preplate layer does not split correctly into layer I and the subplate. Signaling pathways mediated by reelin include the ApoER2 and VLDLR receptors and the adaptor protein Dab1, in addition to other intracellular pathways (Beffert et al., 2004; D'Arcangelo et al., 1999; Hiesberger et al., 1999; Howell et al., 1997; Sheldon et al., 1997). However, in spite of these considerable molecular advances, the exact function and net effect of reelin in neural migration is still a question of debate.

Is Reelin a Stop or a Permissive Signal? It has been suggested that the extracellular protein reelin, which is concentrated around layer I, acts as a stop signal, essentially because migrating neurons detach from the radial glia as soon as they reach the reelin-containing layer I. Furthermore, migrating neurons do not enter this layer in normal development, whereas they do in some pathological conditions in which this layer has been lesioned and depleted of CR cells (Gressens, 2000; Herms et al., 2004). Finally, reelin has been reported to arrest migration in the developing cortex (Dulabon et al., 2000).

While this notion is attractive and plausible when migrating neurons reach layer I, it does not explain the reeler phenotype. If the only function of reelin were to stop migrating neurons, an accumulation of these cells in the reelin-defective layer I of reeler animals would be expected. On the contrary, in *reeler* mutants, the neurons leave the ventricular zone, migrate abnormally in the intermediate zone and cortical plate, and incorrectly position in the lower layers of the cortex without reaching layer I (Caviness, 1982). These phenotypes strongly suggest that reelin is a positive migration signal required for migrating neurons to successfully reach the upper cortical layers and layer I. This possibility is further supported by the normal exit of migrating neurons from the ventricular zone in the mice that overexpress reelin under the control of the nestin promoter (Magdaleno et al., 2002). Therefore, it remains unclear whether reelin is important for initial neuronal migration from the ventricular zone during development.

Recently, elegant experiments have demonstrated that Dab1 is required for the correct migration of neurons in the cortical plate (Sanada et al., 2004). The loss of Dab1 function or the expression of mutated Dab1 constructs not only stops neurons from reaching layer I but also noticeably reduces their migration speed and impairs detachment from radial glial cells (Sanada et al., 2004). These experiments imply that reelin, through its intracellular transducer Dab1, has a cell-autonomous effect on migrating neurons to trigger the movement of the migrating cell and the migration process itself. Another possible interpretation of these findings is that reelin may have an attractive effect on the migrating neuron, either directly or indirectly, by anchoring other extracellular diffusible factors. The hypothesis that reelin may act as a permissive factor, or even an attractive cue, for migrating neuroblasts when they cross the cortical plate and the intermediate zone is consistent with the phenotypes of mice that are deficient in reelin and Dab1.

Another point which has gone largely unnoticed is that reelin expression begins in the cortical plate at early stages of development (Alcantara et al., 1998). In mice, for example, reelin is expressed in GABAergic interneurons of layers V and VI from E18 onward, which implies that the migrating neurons that are fated to form layers II-III must pass through a reelin-rich layer before reaching the upper layers. This observation is inconsistent with the notion that reelin acts as a stop signal in vivo, at least while migrating neurons translocate through the cerebral cortex. In hippocampus, migrating neurons must cross the stratum oriens, which is populated by reelin-expressing GABAergic interneurons, before settling in the pyramidal layer (Alcantara et al., 1998; Borrell et al., 1999). Similarly, it has been reported that neurons forming ectopic clusters in layer I migrate into CR cell- and reelin-rich areas (Beggs et al., 2003).

Another possibility is that reelin may function as a detachment factor. For instance, chains of migrating neurons from the rostral migratory pathway detach from each other and from the surrounding glia in cultures treated with reelin (Kim et al., 2002; see also Sanada et al., 2004).

Taking into account all three possibilities, we may envision that reelin may participate in a multistep functional process. During neuronal migration through the intermediate zone and the cortical plate, reelin may positively regulate migration, acting directly on migrating cells either on locomotion, direction, or attraction. Once neurons reach the upper layers, reelin may help to detach the migrating neurons from the radial glia apical processes. It is still possible that after the above processes reelin acts as a stop cue by preventing neurons from entering layer I. The experiments by Dulabon et al. (Dulabon et al., 2000) in which reelin microbeads placed directly in the cortex arrested migration, indicate that migration arrest may occur when these neurons are exposed to elevated concentrations of reelin. Thus, the multiple roles of reelin may be regulated by its different protein motifs and by concentration gradients of the protein.

Is the Role of Reelin a Secondary Effect of the Lack of Preplate Splitting? Given that in the reeler mice the preplate does not subdivide into layer I and a subplate, it has been proposed that the subsequent abnormal neuronal migration is due to the incapability of migrating neurons to enter the preplate in order to form the cortical plate. However, several data indicate that the absence of reelin has a dual effect: in preplate splitting and directly on late-migrating neurons. On one hand, several genetic mouse models, in which CR cell numbers are normal until a certain developmental stage and then decrease because of early neuron death, have been used to study the function of CR cells and reelin in migration, long after preplate splitting. In the p73 and Emx1/2 knockout mice, as well as in many other mutants, abnormal migration and positioning of late-

migrating neurons are noted (Hevner et al., 2001; Lyu and Wang, 2003; Meyer et al., 2004; Meyer et al., 2002; Shinozaki et al., 2002; Wines-Samuelson et al., 2005; Yang et al., 2000). In the nestin-BDNF-mice, which downregulate reelin expression from E14 onward, altered neuronal migration was also observed (Ringstedt et al., 1998). In all of these mouse models, neurons fail to migrate to layer I, and they settle abnormally in the lower cortical layers, similar to the phenotypes observed in the reeler mouse.

Postnatal ablation of CR cells and several lesional approaches applied to layer I, which leads to focal CR cell loss or alterations, provide further evidence that the late loss of reelin expression impairs neuronal migration in a similar way to the reeler mutant mouse (Beggs et al., 2003; Benardete and Kriegstein, 2002; Halfter et al., 2002; Super et al., 2000). In humans, neurodevelopmental lesions to layer I that cause the degeneration of CR cells, among other effects, are often accompanied by abnormal neural migration in the cortical plate (Gressens, 2000). Finally, studies by Tsai and coworkers, which show altered migration behavior of Dab1-defective migrating neurons (Sanada et al., 2004), offer strong evidence that CR cells and reelin are involved in cortical migration, independent of the preplate splitting process.

Do CR Cells and Reelin Control Radial Glia? The apical endfeets of radial glia end in layer I and intermingle with CR cells. Several studies have shown that in the absence of CR cells, there is a decrease in radial glia. For example, the perinatal lesions described above and the p73 and Emx1/2 knockout mice, which have premature CR cell loss, all show a marked decrease in radial glia and the premature transformation of these cells into astrocytes (Lyu and Wang, 2003; Meyer et al., 2004; Shinozaki et al., 2002; Super et al., 2000). Conversely, ectopic CR cells convert cerebellar Bergmann glia into a juvenile, radial phenotype both in vitro and in vivo (Soriano et al., 1997).

At least part of radial glia regulation is mediated by reelin, since radial glia are immature and disorganized and are converted to astrocytes prematurely, although they are present in the reeler mouse (Förster et al., 2002; Hartfuss et al., 2003; Pinto-Lord et al., 1982). Similar phenotypes have been described in the mice deficient in the reelin receptors ApoER2 and VLDLR (Weiss et al., 2003). Finally, recent data show a preference of astrocytes for reelin-rich stripes in vitro and that reelin triggers Blbp expression in astrocytes (Förster et al., 2002; Frotscher et al., 2003; Hartfuss et al., 2003). All these data point to a clear modulating effect of reelin and CR cells in the organization and life span of radial glia. However, reelin is not required for the appearance of radial glia or for their initial maintenance, as demonstrated by the persistence of radial glia in the reeler mouse.

Whether these effects are direct or indirect and the exact regulatory mechanisms of CR cells and reelin on radial glia remain to be clarified. On one hand, expression of the reelin signaling machinery, including receptors and Dab1, is, to a certain extent, unclear. While the cell bodies of radial glia express little Dab1 mRNA in vivo, Dab1 immunoreactivity has been demonstrated in radial glia processes, which indicates that Dab1 mRNA may be compartmentalized in the radial glia apical processes. There is also similar differences on the expression of reelin receptors in radial glial cell bodies and processes and among cortical regions (Hartfuss et al., 2003; Luque et al., 2003; Magdaleno et al., 2002; Nakamura et al., 2001; Perez-Garcia et al., 2004). Finally, it is also possible that the $\alpha 3\beta 1$ integrin receptors, which may act as reelin coreceptors, may play a role in reelin-dependent regulation of radial glia (Förster et al., 2002; Dulabon et al., 2000; Graus-Porta et al., 2001; Hering et al., 2000). Although the role of integrins as reelin receptors is somewhat controversial, the migratory defects observed in several integrin mutants (Dulabon et al., 2000; Graus-Porta et al., 2001; Schmid et al., 2005) and recent data demonstrating that Dab1-deficient neurons have increased adhesion to radial glial cells (by upregulating $\alpha 3$ integrin at the cell surface), clearly point to a link of cell adhesion in reelin-induced functions in corticogenesis (Sanada et al., 2004). The possibility remains that $\alpha 3$ and $\beta 1$ proteins may require another partner(s) to act as reelin receptors.

Genetic Approaches to CR Cell Function

Recent studies have focused on elucidating the cell biology of CR cells by analyzing their gene expression profiles. In one study, cDNAs from microdissected CR cells were compared with cDNAs expressed in the remaining developing cortex by a subtractive hybridization approach (Garcia-Frigola et al., 2004). In another, a GFP-mouse model was used to isolate CR cells and to characterize their gene expression patterns by microarrays (Yamazaki et al., 2004). In a third study, differential display techniques were used to identify genes with misregulated expression in reeler tissue (Kuvbachieva et al., 2004). These studies have identified a collection of genes that are highly expressed in CR cells, in particular at the specific stage of harvesting analysis. As expected, many of these genes display a dynamic and developmentally regulated pattern of expression in the cerebral cortex and in other brain areas. Some of these genes are metabolic or indicative of early maturation, once again showing that CR cells are highly active, early maturing neurons, even at early stages of development (eg, SAP102, glycogen phosphorylase, or several calcium channel subunits). Another group of genes encode for proteins involved in a variety of signaling pathways, such as Flt3 interacting zinc finger protein 1, protein kinase C inhibitor 1 (pKC1), Gdf5, or regulators of G proteins, among others. This observation opens up the possibility to explore the participation of new signaling systems in CR cell biology and cortical development. In addition, yet another group of genes includes proteins related to cell adhesion, such as two kidney adhesion proteins (podocalyxin and nephronectin), trophinin, or Alex-3, a protein that contains β-catenin domains. Several nuclear proteins and transcription factors, such as CHOP-10, MMUSF, and LIM homeobox proteins 1 and 5, have been also identified. Finally, the molecular approach in reeler tissue has identified several genes with altered expression in the reeler model, one of which is C61, which contains LAG1 and ERM motifs with a putative adaptor function. In the future, these seminal studies are likely to contribute not only to the molecular characterization of CR cells, but

also to the identification of new molecular players in cortical development.

CR Cells in Cortical Networking

Again, Marin-Padilla proposed that CR cells coordinate a primitive synaptic network that controls the maturation of the cerebral cortex, mainly through connections with the apical dendrites of pyramidal cells (Marin-Padilla, 1998). CR cells extend long, tangential axons through layer I, and most, if not all, CR cells are glutamatergic (del Rio et al., 1995; Hevner et al., 2003). They coexist in layer I with an abundant population of GABAergic neurons. Recent studies have shown that CR cells and GABAergic neurons belong to a network of spontaneous neural activity, which is evident from very early stages of development (Aguilo et al., 1999; Radnikow et al., 2002; Schwartz et al., 1998; Soda et al., 2003). Furthermore, neuronal activity in CR cells and GABAergic interneurons appears to be highly synchronized. Both features are maintained in layer I of the reeler cortex, although with significantly decreased synchronized activity, which indicates that the absence of reelin does not disrupt the activity of this neuronal network (Aguilo et al., 1999).

It is clear that GABA and glycine are the main neurotransmitter systems that drive the activity in CR cells (acting as excitatory transmitters at these ages) and that CR cells express the appropriate receptors for these neurotransmitters. However, the participation of glutamate receptors is controversial. While some AMPA and NMDA subunits have been reported to be expressed in CR cells, physiological recordings have detected either important or minor contributions of these receptors in CR cell activity (Kilb et al., 2002; Lu et al., 2001; Mienville and Pesold, 1999; Okabe et al., 2004; Radnikow et al., 2002; Schwartz et al., 1998; Soda et al., 2003). These discrepancies may be related to species-dependent differences or to different ages or recordings. The involvement of metabotropic neurotransmitter receptors has been also shown (Martinez-Galan et al., 2001). Furthermore, both in the neocortex and the hippocampus, CR cells receive direct synaptic input from excitatory afferents (thalamic and entorhinal axons) and from brain stem serotoninergic fibers, indicating a contribution of all these neurotransmitter systems in the synaptic activity driven by CR cells (Janusonis et al., 2004; Super et al., 1998). Cajal-Retzius cell axons appear to establish synaptic contacts on the apical dendrites of pyramidal cells (Radnikow et al., 2002).

Importantly, it remains unclear whether the lack of CR cells or the absence of reelin affects the maturation of the cerebral cortex. The reeler mutation is probably too devastating to draw reliable conclusions on the fine-tuning of cortical maturation or levels of synaptic activity in the developing cortex. To our knowledge, these parameters have not been studied in mouse models that lack CR cells, in many cases because of their perinatal lethality. The generation of conditional murine models that specifically delete CR cells, for example by targeting toxins to these cells, will be required to address whether or not CR cell activity (and that of its GABAergic partners) modulates aspects of cortical maturation. If this were indeed the case, studies would have to focus on processes that occur at early developmental stages, before naturally occurring CR cell death.

CR Cells and Reelin as Targets in Pathology

CR cells are involved in neurological disorders of the human brain associated with migratory defects. Importantly, mutations in the reelin gene account for a human form of an autosomal-recessive lissencephaly (Hong et al., 2000), and both direct and indirect disturbances in layer I and in CR cells are involved in many other focal migration deficits (Gressens, 2000).

In addition, recent evidence has implicated CR cells and reelin in a number of additional neurological disorders, including epilepsy, autism, bipolar disorder, and schizophrenia. Decreased expression of reelin, both at the gene and protein levels, has been consistently observed in the brains of patients affected by schizophrenia and bipolar disorder (Fatemi, 2001; Impagnatiello et al., 1998). Interestingly, this appears to have arisen because of an alteration in the methylation of the reelin gene, as a result of an altered DNA methyltransferase I enzymatic activity (Abdolmaleky et al., 2005; Noh et al., 2005; Veldic et al., 2004). Following this view, decreased levels of reelin expression may have two distinct effects on the brain. On one hand, reelin expressed by Cajal-Retzius cells may account for the migratory deficits detected in the cerebral cortex of schizophrenic patients. Later in development and given the proposed role of reelin in synaptogenesis (Borrell et al., 1999; Liu et al., 2001), decreased reelin expression in interneurons may also explain the decreased number of synapses and dendritic spines observed in the cerebral cortex of these patients (Costa et al., 2001). Reelin is, therefore, a crucial factor in the pathogenesis of these diseases and acts in two critical stages of cortical development, which supports the notion that schizophrenia and bipolar disorders are mainly developmental neurological disorders (Lewis and Levitt, 2002).

Furthermore, decreased reelin expression has been implicated in temporal lobe epilepsy. The hippocampi of medically intractable epileptic patients show a correlation between reelin expression levels and epileptogenesis, as well as with dispersion and misplacement of granule cells in the dentate gyrus (Haas et al., 2002). These studies indicate that decreased reelin expression in the hippocampus not only may alter the pattern of afferent connections but also may lead to the appearance of recurrent mossy fiber collaterals toward the granule cells themselves, thereby forming a reverberant circuit.

Conclusions

Although considerable research effort has been devoted to CR cells, more than a century after their discovery and more than a decade after the discovery of reelin, the function of these cells in cortical development has still not been fully understood. Notably, the precise molecular and cellular mechanisms by which these intriguing neurons regulate the building of the cerebral cortex remain to be elucidated. Part of the complexity is because CR cells do not serve a single function but exert several throughout the distinct stages of development. Because of its size, protein domains, highly dynamic expression pattern, and complex signaling pathway, reelin is designed to exert a range of influences during the stages of cortical development. Furthermore, the participation of reelin in the pathogenesis of neurological disorders suggests that this protein

and its associated signaling pathway may be possible therapeutic targets for the design of therapies addressed to ameliorate these disorders. It is therefore not surprising to learn of a recent study reporting that CR cells in the hippocampus are required for the successful regeneration of axotomized entorhino-hippocampal axons (del Rio et al., 2002).

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